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## ABSTRACT

The aim of this study was to compare the effectiveness of dexamethasone administration following arthrocentesis of the temporomandibular joint (TMJ) with a placebo (saline). Twenty-eight participants with TMJ arthralgia were randomly assigned to two groups of a parallel double-blind RCT. In both groups, an arthrocentesis procedure was carried out. In one group, the procedure was followed by the administration of a single-dose intra-articular dexamethasone. In the other group, saline was administered as a control. Follow-up visits were scheduled after 1, 3, and 24 weeks. During each visit, TMJ pain (on a 100-mm VAS) and jaw stiffness (mouth opening in mm) were scored. In the statistical analysis, generalized estimating equation (GEE) models showed no differences between the two study groups, although pain and jaw stiffness were both reduced over 24 weeks. In conclusion, intra-articular dexamethasone following arthrocentesis did not improve the procedure's effect in patients presenting with TMJ arthralgia (ClinicalTrials.gov number CT01275014).

**KEY WORDS:** TMD, pain, arthralgia, corticosteroids, lavage, RCT.

# Randomized Trial on the Effectiveness of Dexamethasone in TMJ Arthrocentesis

## INTRODUCTION

Orofacial pain can be severe and includes cases of intractable pain as well as acute pain. The most frequent source of orofacial pain is dental disease. Among other sources are musculoskeletal, vascular, neurovascular, and neuropathic disorders. Musculoskeletal sources of orofacial pain are comprised of joint disorders and muscle disorders, although joint and muscle symptoms frequently occur simultaneously. Pain arising from joint disorders is termed 'arthralgia'.

Causes of arthralgia would include mechanical nerve compression secondary to articular disc displacement (Johansson *et al.*, 1990), neurogenic inflammation (Sessle, 1999) secondary to intra-articular changes and synovitis, adhesions, or arthritis. Historically, the displaced disc was considered the primary cause of arthralgia, but the observations that arthroscopy and arthrocentesis of the superior joint compartment reduce or eliminate pain in patients with a permanently displaced disc, without repositioning the displaced disc, have disproved the displaced disc as the cause of arthralgia (Stegenga, 2001). Another possible cause for arthralgia may be mechanical trauma from repetitive extreme loading (*i.e.*, habitual jaw-clenching, bruxism), causing transient hypoxia (Shirakura *et al.*, 2010). The hypoxia may create oxygen-derived free radicals that activate a variety of biochemical changes, leading to arthralgia.

The current treatment modalities focus on alleviating pain and improving function. Arthrocentesis is a minimally invasive procedure aimed at removing inflammatory and pain mediators from the joint cavity solely by the intra-articular flow of saline (Moses *et al.*, 1989; Nitzan and Price, 2001). In addition to arthrocentesis, corticosteroids are commonly added in an attempt to further reduce pain and jaw stiffness (van Oosterhout *et al.*, 2006). Corticosteroids modify the vascular response during the inflammatory process and inhibit enzymes and the actions of inflammatory cells. Their use in the TMJ remains controversial with regard to their efficacy and unknown duration (Wenneberg *et al.*, 1991).

The aim of the current study was to test the additional effect on pain and jaw stiffness of a short-acting corticosteroid (dexamethasone) following an arthrocentesis procedure in the TMJ.

## METHODS

### Participants

Patients referred to the Department of Oral and Maxillofacial Surgery of the University Medical Centre Groningen, with pain in front of the ear or the TMJ area, were asked to participate. All were examined for crepitation and disc

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displacements by means of anamnesis, the presence of articular sounds, and deviation/deflection in full-mouth opening. Radiographic images (panoramic, transpharyngeal, and transcranial) were made to visualize the existence of tissue alterations.

Inclusion criterion were

- (I) History positive for all of the following:
  - (a) In the preceding month, ongoing pain in the face, jaw, temple, in front of the ear, or in the ear, and:
  - (b) Pain provocation on active mandibular movement to all directions (opening, right or left lateral movements, or protrusive).
  - (c) Provocation of the pain on palpation of the lateral pole or around the lateral pole of the condyle.

and

- (II) Complete remission of the reported pain 10 min after the administration of local intra-articular anesthesia [by injection of 0.1 mL articaine 40 mg/mL (Ultracain forte, Aventis Pharma, Hoevelaken, The Netherlands) into the upper joint cavity] (Tjakkes *et al.*, 2007).

Exclusion criteria were:

- past history of open surgery in the affected joint,
- known polyarthritis or rheumatoid arthritis,
- age under 18 yrs,
- ankylosis of the TMJ, and
- self-reported pregnancy.

All participants were informed about their condition and were prescribed Ibuprofen 600 mg three times a day for a seven-day period. After 2 wks, a recall visit was scheduled. Patients who appeared to be symptom-free during that recall were excluded from the study.

Full oral and written information about the treatment and the purpose of the study was provided to all participants. All participants signed informed consent. The local Medical Ethical Committee provided full approval for the study protocol under number 14439. US National Institutes of Health clinical trial registration was done at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (number NCT01275014).

## Randomization

A parallel double-blind RCT was used as study design. Twenty-five notes with the words “isotonic saline” and 25 notes with the word “dexamethasone” were printed and were put into 50 identical and non-transparent envelopes according to a random sequence, which was generated by an independent co-worker using a randomization software package (Statsdirect version 2.7.7, StatsDirect Ltd., Cheshire, UK). Each envelope contained one note, and all envelopes were irreversibly sealed, only to be opened by a third and independent person in a closed room, separated from the operating room, just 1 min prior to the arthrocentesis procedure (see below), thus ensuring allocation concealment. No one else was able to see the contents of the note, and the person who had read the note prepared a blank transparent syringe with either 1 cc of transparent dexametha-

sone or an equal amount of saline, according to the note's information, thus allocating the participant to the intended treatment group. A syringe containing dexamethasone appeared identical to a syringe containing saline, since both fluids are completely colorless and have identical viscosity. The syringe was then handed to the oral surgeon without information on its contents.

Immediately after the syringe was prepared, the note was destroyed, and its contents were not communicated to anyone. At the end of the study, the remainder of the notes were destroyed.

In the control group, four men and 10 women were included; the intervention group consisted of one man and 13 women (see Table 1 and Fig. 1).

## Arthrocentesis Procedure

The arthrocentesis procedure was performed with the participants under local anesthesia and took place in a closed operating room under controlled conditions. After the points for needle insertion were marked, the first 18-gauge injection needle was inserted into the upper intra-articular space of the TMJ. Correct positioning of the needle was determined by saline injection and aspiration. Subsequently, a second 18-gauge needle was inserted into the upper joint space about 8 to 10 mm anterior of the first needle. We confirmed correct positioning of the second needle by allowing injected saline to leave the joint through the first needle. After the needles were positioned, one needle was connected to a medical infusion system to allow isotonic saline (37°C) to enter the upper joint compartment passively. The other needle was connected to an outflow tube to allow the fluid to exit the joint. In about 15 min, approximately 300 mL saline passively flushed the joint. Thereafter, the inflow was stopped, and the prepared syringe (see ‘Randomization Procedure’) that contained either dexamethasone or saline was connected to the inflow needle. In this way, either 1 cc of dexamethasone or an equal amount of saline was washed through the joint in a blinded way. At the end of the procedure, the needles were removed from the joint, and after hemostasis by compression (if necessary), the skin overlying the TMJ was covered with a sterile adhesive plaster.

All patients were then instructed to avoid TMJ loading by following a soft diet for at least 2 wks, then gradually advancing to more tough food. In addition, ibuprofen 600 mg 3dd was prescribed for the first 2 to 5 days to reduce any post-operative pain. All procedures were performed by one surgeon (BS).

Follow-up visits were scheduled after 1 (T1), 3 (T2), and 24 (T3) wks.

## Outcomes

The primary outcome variables were TMJ pain at rest and during mandibular movements [measured on a 100-mm Visual Analogue Scale (VAS), limited by “no pain” and “worst pain imaginable”] and the maximal interincisal opening (MIO, measured in millimeters).

A secondary outcome variable was function impairment [assessed with the Mandibular Function Impairment Questionnaire (MFIQ)]. The MFIQ is a questionnaire assessing, on a five-point

**Table 1.** Description and Comparison of the Control and Intervention Group at Start of the Study

Variable	Control Group (placebo, n = 14)	Intervention Group (dexamethasone, n = 14)
	Mean (95%CI)	Mean (95%CI)
Age, yrs	33.9 (27.0 - 40.9)	32.6 (23.7 - 41.6)
Pain on mandibular movement (mm VAS)	53.4 (43.3 - 63.4)	47.4 (34.4 - 60.3)
MFIQ	52.3 (47.7 - 56.8)	52.8 (47.1 - 58.5)
Max opening	35.1 (30.0 - 40.3)	39.1 (35.2 - 42.9)
SCL-90 Dutch [Arrindell & Ettema (2003)]		
Anxiety	13.7 (10.2 - 17.4)	14.2 (11.4 - 17.1)
Agoraphobia	7.6 (6.5 - 8.8)	8.4 (7.2 - 9.7)
Depression	25.7 (17.4 - 34.1)	23.4 (17.1 - 29.6)
Somatization	19.5 (15.5 - 23.5)	19.7 (15.1 - 24.4)
Cognitive-performance deficits	15.7 (9.9 - 21.5)	13.8 (11.3 - 16.3)
Interpersonal sensitivity and mistrust	23.7 (19.5 - 28.9)	23.9 (20.4 - 27.3)
Acting-out hostility	7.0 (6.2 - 7.8)	7.2 (6.2 - 8.3)
Sleep difficulties	5.7 (4.1 - 7.3)	5.2 (3.4 - 7.0)
Other complaints	4.9 (2.1 - 7.7)	6.4 (3.7 - 9.0)
General psychological distress/psycho-neuroticism	122.8 (92.8 - 152.8)	122.3 (100.1 - 144.5)

scale, an individual's discomfort while performing mandibular functions and during eating of food with different consistencies (range, of 0-68) (Stegenga *et al.*, 1993a; Kropmans *et al.*, 1999). The assessments of TMJ pain, MIO, and MFIQ were carried out on the day of the surgical procedure (T0), and at T1, T2, and T3, by one person (LS).

### Statistical Procedures

Data analysis was executed in such a way that the analyst (JHS) could not observe the control or the intervention group in the dataset. The statistical analysis used 'generalized estimating equation' (GEE) models. By the application of GEE, relationships between and among variables at different time-points are analyzed simultaneously.

For all analyses,  $\alpha = 0.05$ . All procedures were executed in Stata version 10.1 SE (Stata Corp., College Station, TX, USA). The sample consisted of 28 participants ( $\beta = 0.8$ ;  $f = \text{estimated } 0.3$ ).

### RESULTS

All patients had complete remission of the reported pain within 10 min after the administration of local intra-articular anesthesia into the upper joint cavity. Over time, in both groups, the TMJ pain (mm VAS) declined, MIO improved, and the MFIQ score decreased (see Figs. 2a-2c). GEE models were created for the outcome variables TMJ pain, MIO, and MFIQ. For all analyses, the first predictor variable to be entered into the model was treatment group (placebo, as reference, *vs.* dexamethasone). The hypothesis of interest was whether the pattern of the progression of the outcome over time differed between treatment groups. Hence, the hypothesis involved testing the interaction between time and treatment group, *i.e.*, a model of  $Y = \beta_0 + \beta_1 \cdot \text{treatment\_group} + \beta_2 \cdot \text{time} + \beta_3 \cdot \text{time} \cdot \text{treatment\_group}$ , with the hypothesis  $H_0: \beta_3 = 0$  tested.

Table 2 shows the estimated regression coefficients ( $\beta$ ) for the variables treatment group, time, and their interaction for these models. The analyses showed that the treatment group had no relationship with all outcome variables, and therefore, no other predictors, confounders, or effect modifiers were entered into the model.

The achieved *post hoc* power ( $1 - \beta$  error probability) for TMJ pain was 0.09 ( $f = 0.11$ ); for MIO, it was 0.09 ( $f = 0.11$ ).

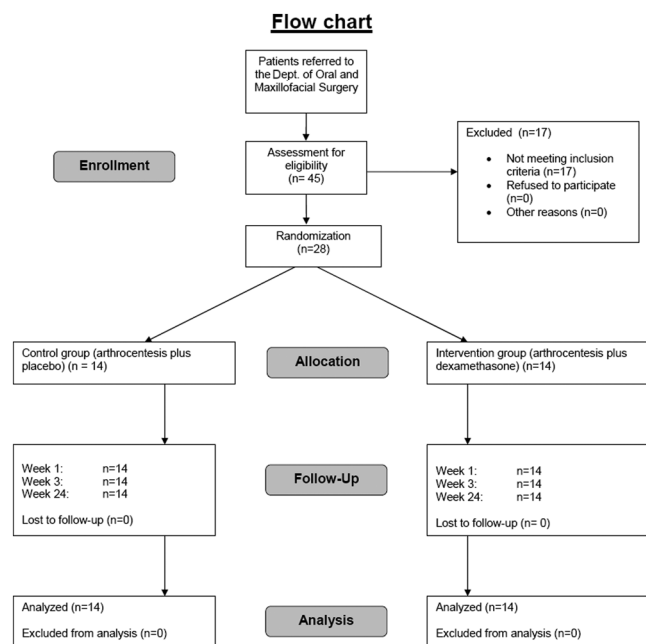
### DISCUSSION

The main findings from this study were that the administration of dexamethasone following an arthrocentesis procedure did not appear to have a significant additional effect on overall pain reduction.

Strengths of the study were that this was a double-blind trial on the additional use of a steroid after arthrocentesis. Additional steroids in arthrocentesis are used in clinical settings, but evidence for their use is lacking. The main weakness of the trial was its small sample size.

Because of the relatively few samples, a type II statistical error may be a typical explanation for this finding. A common way to reduce random error in, or increase the precision of, an estimate is to enlarge the size of the study. Yet, a problem in planning study size is determining how to balance the value of greater precision in study results against the greater costs. Solving the problem thus involves a cost-benefit analysis of expending greater effort or funds to gain greater precision. Greater precision has a value to the beneficiaries of the research, but the value is indeterminate, because the number of beneficiaries is always uncertain. If the study had more patients, it is theoretically possible that the results could change, since the next "set" of patients could have a different response and thus outcome. If so, the total number of participants needed to demonstrate a clinical effect of dexamethasone becomes so large

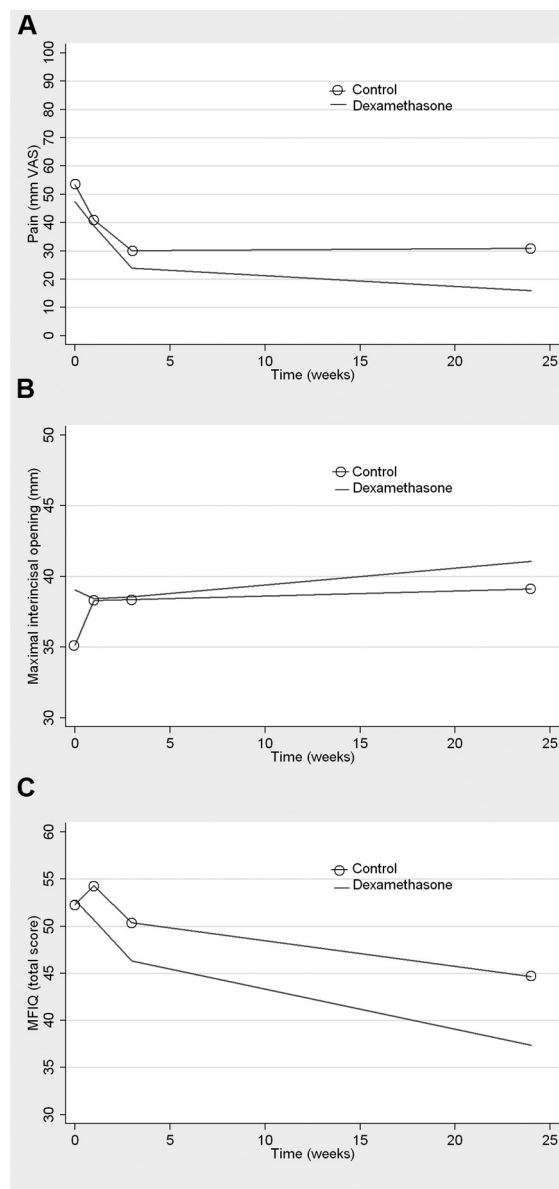




**Figure 1.** Patient flow chart and disposition of the participants.

that the net effect (*i.e.*, the additional effect of dexamethasone) is clinically of minor importance compared with the effect of arthrocentesis. Arthrocentesis by itself has been shown to improve MIO and to reduce pain over time when it is compared with other therapies (*e.g.*, physical therapy, splint therapy; Stegenga *et al.*, 1993b; Goudot *et al.*, 2000; Schiffman *et al.*, 2007; Dıraçoğlu *et al.*, 2009). In our study, the effect of arthrocentesis thus clearly overpowered any effect of dexamethasone. Thus, administering additional dexamethasone following arthrocentesis of the TMJ will most probably result in an outcome similar to that achieved by arthrocentesis without additional dexamethasone.

Normally, the pressure-bearing articular surfaces of the TMJ are non-innervated and cannot produce sensory input or nociception. Proprioceptive input needed for functional guidance comes from the proprioceptors located in the muscles and ligaments (Hannam and Sessle, 1994). TMJ arthralgia primarily originates from the joint ligaments (*i.e.*, capsule and disc attachments) and the subchondral bone. Ligamentous receptors are high-threshold mechanoreceptors that are stimulated when the ligament is stretched beyond its functional range. However, inflammatory mediators may lower the pain threshold, making nociceptors more sensitive to stimulation. As a result, stimulation from normal functioning may initiate sensations of discomfort. Arthralgia usually exerts a protective inhibitory influence on biomechanical activity, due to altered proprioceptive sensory or nociceptive input to the central nervous system. Usually, a primary insult, whether (bio)mechanical, biochemical, inflammatory, or immunologic, disturbs the intra-articular balance between synthesis and degradation (Stegenga, 2001). Early



**Figure 2.** Plots of the the TMJ pain (mm VAS), maximal interincisal opening, and MFIQ over time. Baseline data can be found in Table 1. After 1 wk, the TMJ pain was reduced to 41.0 (28.4 – 53.6) mm VAS (95% CI) and 38.9 (21.9 – 55.8) mm VAS (95% CI) for, respectively, the control group and the dexamethasone (intervention) group (A). At 3 wks, the VAS values of the TMJ pain were 30.0 (13.1 – 47.0) mm and 23.9 (13.1 – 34.6) mm, respectively. At 24 wks, the pain was stable at 30.9 (10.1 – 51.7) mm VAS and 16.0 (1.2 – 30.8) mm VAS, respectively. At that point (24 wks), the maximal interincisal opening (95% CI) was 39.1 (33.4 – 44.8) mm and 41.0 (36.2 – 45.9) mm for, respectively, the control group and the dexamethasone (intervention) group (B). The MFIQ (95% CI) at 24 wks was 44.6 (33.9 – 55.4) and 37.4 (28.0 – 46.7) for, respectively, the control group and the dexamethasone (intervention) group (C). In the control group, four men and 10 women were included; the intervention group consisted of one man and 13 women (see Table 1). There were no statistically significant differences between the intervention group and the control group for all outcome variables (see Table 2).

**Table 2.** Regression Coefficients and 95% Confidence Intervals as Derived from GEE Analyses

GEE Analysis			
Model	Determinant	Regression Coeff. (95% CI)	p
Pain on mandibular movement (mm VAS)	Treatment	-4.2 (-18.6 – 10.3)	0.57
	Time	-0.5 (-1.2 – 0.1)	0.10
	Time * Treatment	-0.4 (-1.3 – 0.4)	0.32
Maximal interincisal opening (mm)	Treatment	1.5 (-3.8 – 6.8)	0.58
	Time	0.1 (-0.1 – 0.2)	0.22
	Time * Treatment	0.0 (-0.2 – 0.2)	0.91
MFIQ	Treatment	-2.0 (-10.5 – 6.4)	0.64
	Time	-0.3 (-0.7 – -0.0)	0.05
	Time * Treatment	-0.2 (-0.7 – 0.2)	0.33

The regression coefficients represent the longitudinal relationship for the outcome variables 'Pain on mandibular movement', 'Maximal interincisal mouth opening', and 'MFIQ' and their determinants.

changes in the joint cannot be diagnosed validly by radiographic imaging, because early pathology may escape radiological detection (Milam, 2005). Radiographic imaging will reveal only the cases later in the disease, when remodeling or internal derangements are shown. The objectives for managing the condition are to re-establish the balance between synthesis and breakdown and to optimize the circumstances for repair and healing. These objectives can be achieved by controlling overloading, improving function, and reducing pain. As such, therapy focuses on reassurance, instructions, anti-inflammatory medication, and arthrocentesis to control the pain. By flushing the TMJ, as is done in arthrocentesis, the degradative components are cleared from the joint, and this may be the reason arthrocentesis by itself has a therapeutic effect in a reduction of pain.

Dexamethasone modifies the vascular response during the inflammatory process and inhibits both destructive enzymes and the actions of inflammatory cells (Smith *et al.*, 2003). It has been suggested that this decrease in inflammatory potency of the synovial fluid would result in greater pain reduction, but this study showed that the effect of dexamethasone contributed in a minor way to that effect, if at all.

Because of small sample sizes, this study was also unable to identify any side-effects of dexamethasone. One uncertainty is the unknown working time of dexamethasone in the TMJ. Its half-life of 36 to 72 hrs makes it unlikely that long-term effects can be expected. Our analyses also did not suggest a long-term effect. However, these half-life effects do not count for all corticosteroids. Kenacort, for example, has a longer half-life and may have a longer lasting effect as compared with dexamethasone. Kenacort, however, is opaque white and is more difficult to test in a double-blind fashion. We tested an opaque syringe, but the problem was that droplets of Kenacort were regularly spilled while the syringe was being connected to the needles, thus revealing the contents. To our knowledge, no RCTs exist addressing the long-term effect of Kenacort.

In conclusion, intra-articular dexamethasone following an arthrocentesis procedure did not improve the effect of the arthrocentesis in patients presenting with TMJ arthralgia.

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